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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/928,198	08/10/2001	James Arthur Hoffmann	X12383N	6700

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/928,198	HOFFMANN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *128* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *128* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/20/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

Receipt is acknowledged of a request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e) and a submission, filed on 20 October 2003. The submission, however, is not fully responsive to the prior Office action because continued examination under 37 CFR 1.114 does not apply to an application unless prosecution in the application is closed. Since the RCE was accompanied by a reply to a non-final Office action, the reply will be entered and considered under 37 CFR 1.111.

The amendment filed 20 October 2003 has been entered in full. Claims 1-127 were cancelled. New claim 128 was added. Claim 128 is under examination.

The information disclosure statement filed 20 October 2003 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection of claim 119 under 35 U.S.C. 112, first paragraph, new matter, as set forth at page 3 of the previous Office Action 14 April 2003, is *withdrawn* in view of the amendment 20 October 2003.

The rejection of claim 104 under 35 U.S.C. 102(b) as being anticipated by Hirai *et al.*, US Patent No. 4,659,696, as set forth at page 4 of the previous Office Action 14 April 2003, is *withdrawn* in view of the amendment 20 October 2003.

The rejection of claims 105-111, 116-127 under 35 U.S.C. 103(a) as being unpatentable over Hirai *et al.*, US Patent No. 4,659,696 in view of Skrabanja *et al.*, EP 0853 945 A1 (cited in IDS, reference #BF) as set forth at pages 4-6 of the previous Office Action 14 April 2003, is *withdrawn* in view of the amendment 20 October 2003.

The rejection of claims 112-115 under 35 U.S.C. 103(a) as being unpatentable over Hirai *et al.*, US Patent No. 4,659,696 and Skrabanja *et al.* EP 0853 945 A1 and further in view of Boime *et al.* US Patent No. 6,238,890 (cited in IDS, reference #AR) as set forth at pages 6-7 of the previous Office Action 14 April 2003, is *withdrawn* in view of the amendment 20 October 2003.

The provisional rejection of claims 104-111 and 120-127 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 62-78 of copending Application No. 09/973918 in view of Andya *et al.*, US Patent No. 6,267,958 B1 as set forth at pages 9-11 of the previous Office Action 14 April 2003, is *withdrawn* in view of the amendment 20 October 2003.

The provisional rejection of claims 112-115 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 62, 67, 68, 73, 74 of copending Application No. 09/973918 in view of Boime *et al.*, US Patent No. 6,238,890 as set forth at pages 12-13 of the previous Office Action 14 April 2003, is *withdrawn* in view of the amendment 20 October 2003.

The provisional rejection of claims 116-119 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 62, 67, 68, 73, 74 of copending Application No. 09/973918 in view of Skrabanja *et al.,* EP 0853 945 A1 as set forth at pages 13-14 of the previous Office Action 14 April 2003, is *withdrawn* in view of the amendment 20 October 2003.

The provisional rejection of claims 104-115 and 120-127 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 141-152, 154, 156, 158 of copending Application No. 09/744431 in view of Andya *et al.,* US Patent No. 6,267,958 B1 as set forth at pages 14-15 of the previous Office Action 14 April 2003, is *withdrawn* in view of the amendment 20 October 2003.

The provisional rejection of claims 116-119 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 141, 142, 153,155-157 of copending Application No. 09/744431 in view of Skrabanja *et al.,* EP 0853945 A1 as set forth at pages 16-17 of the previous Office Action 14 April 2003, is *withdrawn* in view of the amendment 20 October 2003.

Matter of Record

Applicants have addressed the rejections of claims 104-127 in the instant amendment. Because claims 104-127 were cancelled, the Examiner will address Applicants' argument only if it applies to claim 128.

Claim Rejections - 35 USC § 103

Claim 128 is rejected under 35 U.S.C. 103(a) as being unpatentable over Keene *et al.*, The Journal of Biological Chemistry Vol. 264/9: 4769-4775 (1989) in view of Skrabanja *et al.*, EP 0853 945 A1 (cited in IDS, reference #BF) and Andya *et al.*, US Patent No. 6,267,958 B1 (cited in last Office Action).

The instant claims are drawn to a pharmaceutically acceptable solution formulation comprising human FSH (concentrations 5.0ug/ml to 2mg/ml) and benzyl alcohol in an aqueous diluent, wherein the FSH consists of an α-subunit having SEQ ID NO:5 and a β-subunit having SEQ ID NO:6 held together by noncovalent interactions and wherein the formulation is suitable for multi-dose administration by injection.

Keene *et al.* teach the expression of biologically active recombinant human FSH (abstract, page 4769, 3rd paragraph; page 4771, 3rd paragraph and 6th paragraph). Human FSH α subunit is SEQ ID NO:5 (1-92 amino acids). Human FSH β subunit is SEQ ID NO:6 (1-111 amino acids). SEQ ID NO:11 is human FSH β subunit, but 3 amino acids shorter than SEQ ID NO:6. Keene *et al.* describe the construction and expression of human FSH α and β subunit (page 4770, first paragraph). Keene *et al.* teach the biological activity of recombinant human FSH (page 4772, 2nd paragraph-page 4773 and Figures 6, 7). Keene *et al.* do not disclose pharmaceutical formulations of recombinantly expressed human FSH with benzyl alcohol suitable for multi-use administration by injection.

Skrabanja *et al.* teach a stable pharmaceutical formulations comprising liquid FSH (abstract; page 3, lines 15-18, 35-38 and page 4, lines 11-13). Liquid FSH

comprises all forms including human recombinant FSH (page 3, lines 35-54). Skrabanja *et al.* teach concentrations of FSH which overlap the concentrations in the instant claims (page 5, lines 5-14). Skrabanja *et al.* teach an article of manufacture comprising a vial or a pen-injector device. The formulation can be in the form of a cartridge for multiple uses (page 5, lines 21-45).

Andya *et al.* teach stable lyophilized protein formulations which when reconstituted generates a stable multi-use formulation (column 1, lines 52-column 2, line 9). The reconstituted formulation may be used as a multi-use formulation (column 2, lines 20-30). Andya *et al.* teach the follicle-stimulating hormone (FSH) as a suitable protein in the formulation (column 6, lines 44-50). Andya *et al.* teach that a preservative can be added to the diluent to reduce bacterial action in the reconstituted formulation, thus facilitating the production of a multi-use reconstituted formulation. Examples of preservatives include benzyl alcohol and m-cresol (column 9, lines 46-58).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Reddy, Skrabanja and Andya to make the instant invention of stable, pharmaceutical acceptable, solution formulation suitable for multi-use comprising FSH and benzyl alcohol. The motivation and expected success is provided by Skrabanja and Andya. Skrabanja *et al.* teach pharmaceutical formulations comprising FSH which can be used in stable multi-use liquid pharmaceutical formulations. Andya *et al.* teach that pharmaceutical multi-use formulations comprising FSH can have preservatives such as benzyl alcohol to reduce bacterial action.

Applicants argue that Skrabanja does not express or imply any desire to provide a preserved formulation. Applicants contend that Skrabanja discloses a sterile aqueous solution of FSH which may be provided in a cartridge containing one or more therapeutic doses. Applicants state that neither sterility nor one or more doses necessarily suggest the use of a preservative. Applicants contend that sterility refers to the condition of the solution when the cartridge is sealed, it does not indicate the use of an antimicrobial preservative. Applicants argue that Skrabanja provides not information on how long the sterile solution can be safely used and does not hint that preservative could be used in its solution formulations.

Applicants' arguments have been fully considered but are not deemed persuasive. When relying on a combination of two or more references to establish a prima facie case of obviousness, the PTO must show that there is some suggestion or motivation to combine the prior art references. This suggestion or motivation can be found in the prior art references themselves, *in the knowledge generally available to one skilled in the art* or, in some cases, from the nature of the problem to be solved. The addition of preservatives to pharmaceutical formulations is deemed routine and well within the purview of the skilled artisan. Furthermore, Andya teaches the use of various preservatives in FSH pharmaceutical formulations.

Double Patenting

Claim 128 is provisionally rejected under the judicially created doctrine of double patenting over claims 159 and 160 of copending Application No. 09/744,431 in view of

Keene *et al.*, The Journal of Biological Chemistry Vol. 264/9: 4769-4775 (1989), Skrabanja *et al.*, EP 0853 945 A1 (cited in IDS, reference #BF) and Andya *et al.*, US Patent No. 6,267,958 B1 (cited in last Office Action).

Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claim is drawn to a pharmaceutically acceptable solution formulation comprising human FSH (concentrations 5.0ug/ml to 2mg/ml) and benzyl alcohol in a aqueous diluent, wherein the FSH consists of an α-subunit having SEQ ID NO:5 and a β-subunit having SEQ ID NO:6 held together by noncovalent interactions and wherein the formulation is suitable for multi-dose administration by injection.

Claims 159 and 160 of copending application 09/744,431 are drawn to a pharmaceutically acceptable solution formulation comprising human FSH (concentrations 5.0ug/ml to 2mg/ml) and a preservative in an aqueous diluent, wherein the preservative is selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkyparaban, benzalkonium chloride, benzethonium chloride, sodium dehydroacetate, thimerosal, and mixtures thereof, wherein the FSH consists of an α-subunit having SEQ ID NO:5 and a β-subunit having SEQ ID NO:6 held together by noncovalent interactions and wherein the formulation is suitable for multi-dose administration by injection.

The claim in the instant application and in copending application 09/744,431 overlap in scope in that they both recite pharmaceutical compositions comprising FSH (5.0 ug/ml to 2mg/ml) and benzyl alcohol. Keene *et al.* teach the recombinant expression of human FSH comprising α-subunit (SEQ ID NO:5) and a β-subunit (SEQ

ID NO:6 and SEQ ID NO:11) held together by noncovalent interactions. The motivation and expected success is provided by Skrabanja and Andya. Skrabanja *et al.* teach FSH in stable multi-use liquid pharmaceutical formulations. Andya *et al.* teach that pharmaceutical multi-use formulations comprising FSH and benzyl alcohol.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
3/9/04